

REMARKS

Claims 15-28, 33 and 38-46 have been canceled without prejudice or disclaimer. Claims 47-76 have been added and therefore are pending in the present application. Claims 47-76 are supported throughout the specification, including the original claims. For example, claims 72-75 are supported by page 13, lines 9-14 of the specification.

The specification has been amended to add sequence identifiers in the brief description of the figures and to delete a hyperlink.

An abstract of the disclosure has been amended to address the objection made by the Examiner.

The title of the invention has been amended to more accurately define the claimed invention.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Objection to Claims 15, 16, 18, 27, 38, 39 and 41

The Office objected to claims 15, 16, 18, 27, 38, 39 and 41 for poor grammar. Claims 15, 16, 18, 27, 38, 39 and 41 have been canceled without prejudice or disclaimer. Therefore, the objection is rendered moot.

II. The Rejection of Claims 15, 16, 18, 27, 33, 38, 39 and 41 under 35 U.S.C. 101

Claims 15, 16, 18, 27, 33, 38, 39 and 41 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the Office stated that "The variant of SEQ ID NO: 2 having a H144R substitution is likely to occur in nature." This rejection is respectfully traversed.

The present invention is directed to variants of a parent RP-II protease, comprising a modification at one or more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201. Thus, the present invention is not directed to products occurring in nature.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 101. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 16, 18, 27, 33, 39 and 41 under 35 U.S.C. 112

Claims 16, 18, 27, 33, 39 and 41 are rejected under 35 U.S.C. 112 as being indefinite. Specifically, the Office objected to the following:

1. The phrase “where the positions refer to BLC or corresponding positions” recited in claim 16;
2. The phrase “144 and or 161” recited in claim 18;
3. The lack of a reference to a specific sequence in claims 18, 39 and 41;
4. The phrase “produced in claim 15” recited in claim 33;
5. The phrase “the modification is ... of BLC” recited in claims 39 and 41;
6. The lack of antecedent basis for the phrase “The RP-II protease of claim 15” recited in claim 27; and
7. The lack of antecedent basis for the phrase “a RP-II protease variant ... in claim 15” recited in claim 33.

Claims 15-28, 33 and 38-46 have been rewritten as claims 47-76 to address this rejection. Applicants therefore submit that this rejection has been overcome. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. The Rejection of Claims 15, 16, 18, 27, 33, 38, 39 and 41 under 35 U.S.C. 112

Claims 15, 16, 18, 27, 33, 38, 39 and 41 are rejected under 35 U.S.C. 112 “because the specification ... does not reasonably provide enablement for any variant of any RP-II protease comprising any modification within 10 angstroms of the ion-binding site.” This rejection is respectfully traversed.

It is well settled that “[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.” *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Moreover, “a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 169 U.S.P.Q. at 369.

“The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the

invention and the state of the art ... The test is not quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed ..." *Ex parte Jackson*, 217 U.S.P.Q. 804 (Bd. Pat. App. 1982).

It is also well settled that an assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). See also *U.S. v. Telectronics*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974); *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (BPAI 1988).

Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

Applicants submit that the specification enables the claimed invention. The claimed invention is directed to variants of a parent RP-II protease, comprising a modification at one or more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201, wherein the variant has RP-II protease activity. The specification contains an extensive disclosure of the variants of the present invention and methods for producing the polypeptides.

Application of the *Wands* factors to these facts further supports the conclusion that the claims are enabled. First, the present invention is in the field of molecular biology. The *Wands* court has already held that the level of skill in this art is high. *Wands*, 858 F.2d at 740. Second, the specification provides an extensive disclosure for producing the claimed polypeptide. Third, as in *Wands*, the methods of making the claimed polypeptides and screening for RP-II protease activity are known in the art and described in the specification. Fourth, the specification discloses a number of parent RP-II proteases (SEQ ID NOs: 2, 4, 6, 8, 10, 12 and 14) and numerous variants within the scope of the claims. Fifth, given the extensive guidance given in the specification and the high level of skill in the art, the experimentation involved to produce other variants within the scope of the claims is routine and well within the skill of those in the art. As held by the *Wands* court, "The test is not merely quantitative since a

considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed.” *Id.* at 737.

As of Applicants’ effective filing date, persons of ordinary skill in the art were able to routinely produce thousands of RP-II protease variants comprising a modification at one or more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201. Moreover, the specification discloses a number of other positions which can be mutated.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. The Rejection of Claims 15, 16, 18, 27, 33, 38, 39 and 41 under 35 U.S.C. 112

Claims 15, 16, 18, 27, 33, 38, 39 and 41 are rejected under 35 U.S.C. 112 for failing to comply with the written description requirement. This rejection is respectfully traversed.

As set forth in Federal Circuit decisions, a specification complies with the written description requirement if it provides “a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials.” See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

The claimed invention is directed to variants of a parent RP-II protease, comprising a modification at one or more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201, wherein the variant has RP-II protease activity. The specification describes a number of other positions, including specific mutations, which can be combined with any of the claimed modifications. Thus, the specification fully describes the RP-II protease variants of the present invention.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. The Rejection of Claims 15, 16, 18, 27, 33, 38, 39 and 41 under 35 U.S.C. 102

Claims 15, 16, 18, 27, 33, 38, 39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Norregaard-Madsen et al. (WO 01/16285). This rejection is respectfully traversed.

Norregaard-Madsen et al. disclose RP-II proteases and variants thereof. However, Norregaard-Madsen et al. do not disclose RP-II proteases, comprising a modification at one or

more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201, as claimed herein.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. The Rejection of Claims 15, 16, 18, 38 and 39 under 35 U.S.C. 102

Claims 15, 16, 18, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Sloma et al. (*J. Bacteriol.* 172: 1024-1029 (1990); UniProt database Acc. No. MPR-BACSU (1995)). This rejection is respectfully traversed.

Sloma et al. disclose a wild-type metalloprotease from *Bacillus subtilis*. However, Sloma et al. do not disclose RP-II proteases, comprising a modification at one or more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201, as claimed herein.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

VIII. The Rejection of Claims 15, 16, 18, 38 and 39 under 35 U.S.C. 102

Claims 15, 16, 18, 38 and 39 are rejected under 35 U.S.C. 102(a&e) as being anticipated by Ostergaard et al. (U.S. Patent No. 6,558,939; Alignment with SEQ ID NO: 2). This rejection is respectfully traversed.

Ostergaard et al. is a US equivalent to Norregaard-Madsen et al. discussed in Section VI above. As explained therein, Ostergaard et al. do not disclose RP-II proteases, comprising a modification at one or more positions selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201, as claimed herein.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

IX. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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